

UNITED STATES PATENT OFFICE

2,512,192

SILICONE RESIN MEDICAMENT COATING

Ernest C. Yen and Frank E. Stirn, Pearl River,
N. Y., assignors to American Cyanamid Com-
pany, New York, N. Y., a corporation of Maine

No Drawing. Application May 26, 1948,
Serial No. 29,407

4 Claims. (Cl. 167—82)

1

Our invention relates to a coating, and a method for coating such medicaments as capsules, pills and tablets whereby these medicaments are protected from moisture and/or oxygen or other substances with which they come in contact which tend to cause variations in their medicinal value, and at the same time, the escape of materials in said medicaments is prevented.

In the past there has been a considerable field for development in the production of soft gelatin capsules containing various substances. Certain of these substances, particularly thiamin, vitamin A, vitamin D, vitamin E and liver concentrates, have an odor which escapes through the walls of the gelatin capsule and is not particularly desirable. At the same time oxygen from the air and moisture can penetrate the gelatin shell causing a gradual decrease in potency of the contents of the gelatin capsules. When these gelatin capsules are filled with dry powders certain of the powders tend to react with each other or the gelatin of the shell in the presence of moisture causing black spots, thus giving rise to a product which meets consumer resistance.

In the past certain enteric coatings have been used such as shellac or gum sandarac, etc., for the purpose of protecting capsule contents from the acid of the stomach, and which disintegrate under the conditions of the intestines. In contrast thereto we have found that by using our superior type of coating it is possible to coat a gelatin capsule or nearly any of the normal commercial tablets or pills with a thin coating of a silicone resin whereby these objects are re-enforced mechanically, resist abrasion, possess a clean, polished, pleasing appearance, are more resistant to moisture, oxygen and other deleterious substances, and at the same time retain their potency longer.

As an object of our invention there is provided a coating for tablets or shells which gives a comparatively high gloss, smooth finish and non-dusting film, which meets with ready consumer acceptance, insures the constancy of the dose, and markedly decreases the number of broken, nicked and defective tablets. Tablets which are sold in drug stores in bottles, such as some grades of aspirin, cough tablets, bicarbonate of soda pills, anti-acid pills and many others, have a tendency to dust by frictional contact whereby portions of the exterior surface are broken away. This gives a nicked appearance to the tablet, cuts down on the volume of the tablet so that the dosage is no longer uniform, and leaves a dust or powder in the container which is aesthetically

2

undesirable and meets with consumer resistance. Our protective coating re-enforces the surface layers of the tablets so that this dusting, crazing, cracking and surface disintegration is prevented, the tablets maintain a uniform size of dose, are more pleasing aesthetically and are but slightly, if any, slower in decomposing; so that the tablets will not disintegrate in the bottle but yet will disintegrate without an appreciable change in time in the mouth or stomach, releasing the therapeutic dosage.

Another object of our invention is the protection of soft gelatin capsules where, by coating the gelatin film either internally or externally or both, during the process of manufacture or afterwards, a gelatin shell capsule is produced containing a therapeutic substance, which substance is given greater protection because of this coating, and which gelatin shell is itself protected from the deteriorating influences of materials both within the capsule and externally. As remarkable as it may seem it has been found that by filling a soft gelatin capsule which gelatin shell itself contains considerable moisture with a moisture sensitive substance such as vitamin C, the vitamin C will cause the gelatin shell to show dark spots; but if the gelatin capsule is dried and coated with a silicon film in accordance with this, our invention, the same capsules will maintain a clear, unspotted appearance, even in the presence of high humidity for a prolonged period of time. It is not known how long the contents will thus be protected by the silicon film but extensive tests have been carried out over a period of many months under accelerated ageing conditions without any breakdown in quality. It is expected from such tests that such coated capsules would last without deterioration under average conditions for a period of at least several years, and probably indefinitely.

A further object of our invention is the treating of hard gelatin capsules by coating with a silicon resin whereby the two parts of the gelatin shell are adhesively fastened to each other so that these capsules will stand up under shipping conditions without parting, or the releasing of dust, for prolonged periods. Additionally, the gelatin capsule is protected from the deleterious effects of moisture, atmospheric gases, and other disintegrating agents with which the capsule may come in contact.

Surprisingly, these films while apparently resistant to moisture will not appreciably delay the absorption of the therapeutic materials once in-

gested, and do not leave a residue which is either appreciable or in any way deleterious.

The coating of our new invention comprises a silicon containing resin. It is necessary that the silicon resin be in a form which may be applied as a thin film, which will polymerize, or set to the desired state. For some purposes a sticky or tacky film is useful but normally for greatest commercial acceptance it is desirable that the film form a fairly hard, dry, lustrous, non-tacky, smooth surface. From the standpoint of commercial utility for most pharmaceutical products it is necessary that the film cure to this state without the application of much heat. The amount of heat that can be used, of course, varies with the material in the capsule, pill or tablet, but for many pharmaceutical products, 60° C. is about the limit. Any of the silicon containing resins which are cured under these conditions and which may be applied in thin layers appear to be satisfactory.

The particular silicon resins themselves are not a part of this invention and any of the standard commercial resins may be used. It is not necessary that the material be applied as a liquid, as some of these silicon resin forming materials, such as the General Electric "Drifilms," are volatile and may be applied in the gaseous phase. These materials are among the volatile silicon compounds such as alkyl silicon halides. A material such as dimethyl silicon dichloride is comparatively volatile and may be applied to a gelatin film either direct or by allowing an ethereal solution thereof to evaporate and the vapors contact the gelatin film or tablet.

Frequently, however, it is more convenient to use a liquid preparation. Such preparations are solvent dispersions of "silicone resins," that is partially polymerized products which will polymerize to a silicone resin. For purposes of convenience it is normally easier to purchase the material under trade-names rather than making it, or obtain it to a performance specification. Materials which are sold commercially such as the Dow-Corning silicone "DC 803" or "DC 804" or General Electric's "9980" give highly satisfactory and useful films. To those skilled in the art in silicone compounding it is comparatively simple to select a heat-curable or potentially heat-curable silicone resin, which either from its inherent characteristics, or the addition of a polymerizing agent, will set up or cure without the use of sufficient heat to deleteriously affect the medicinal substance. As a final check to insure the complete removal of all halide to silicon linkages, ammonia fumes may be used. Usually sufficient moisture is present to insure the hydrolysis of the halogen, but ammonia fumes insure a neutral product. If desired silicon containing resins may be used in which the silicon atoms are linked through nitrogen, from ammonia, rather than through oxygen as in the silicones, such resins at times being referred to as silamines.

There are many discussions of methods for preparation of silicon resins. Patent No. 2,306,222 to W. I. Patnode "Method of Rendering Materials Water Repellent," discloses the use of a vapor of an alkyl silicon halide for making glass vapor-proof. The same types of materials as therein described may be used to water-proof, protect and render odorless medicinal compounds. The patent to Safford, No. 2,424,853 and the patent to Tanis, No. 2,408,822, additionally describe siliceous halides and their conversion to

resins. There are several methods of preparing such silicon resins, among the others are the reaction of Grignard type reagents with a silicon tetrahalide. From the standpoint of costs silicon tetrachloride is normally used and the Grignard may be either alkyl or aryl or a mixture thereof. The amounts of each alkyl and aryl used affect the brittleness and rate of cure of the resin formed. Normally the product of the reaction of the Grignard reagent with silicon tetrachloride is allowed to react with moisture, allowed to partially polymerize and the partially polymerized materials are dissolved in a suitable solvent whereby additional polymerization is either inhibited or substantially slowed down. The higher the ratio of lower alkyls, the more rapid the materials will cure and the more brittle will be the film. The more highly branched the chains formed in the resin, which are necessarily formed by the polymerization of the silicone types containing more halide atoms per silicon molecule, the more brittle and polymerized are the resins.

The organo-silicones sometimes referred to as organo-polysiloxanes, more particularly the hydrocarbon substituted polysiloxanes are particularly suitable for coating. The patent to Wright et al., No. 2,389,477, entitled "Polysiloxane Resins" gives considerable information of this type of resin. Certain of the resins which are described in the patent to Hyde, No. 2,386,466, "Insulated Conductor and Insulation Therefor," which if diluted with a solvent may be used in accordance with the instant invention. The patent to Hyde, No. 2,371,050, "Organo-Silicon Polymers and Method of Making Them," describes certain additional methods of preparing such resins. It is not necessary that the resins be prepared from halogen containing compounds as for example, methods such as set forth by Strain et al. in Patent No. 2,394,642, "Silicic Acid Ester," describes a different form of silicon containing resin. The patent to Iler, No. 2,395,550, "Modified Alkyd Resins," describes still further modifications of silicon containing resins in which the silicon linkages are different than those classified as organo-polysiloxanes.

It is not intended that a treatise be here included on the production of such resins, as such resins are the invention of others and are adequately described in the patent literature, as well as elsewhere. The text "Introduction to the Chemistry of the Silicones," Eugene G. Rochow, John Wiley & Sons, Inc., New York, 1946, gives many useful details.

The therapeutic material to be treated with these resins may be treated in the gaseous phase by allowing vapors to contact the materials but are more conveniently prepared by dissolving the silicon resins in solvents such as toluene, isopropyl alcohol, petroleum ether or acetone to the extent of 1% to 10%. The tablets or capsules are then submerged in this solution for a period at least sufficient to allow them to become wetted, and perhaps for periods as long as several minutes, removed from the solution, shaken to remove excess liquid and allowed to dry. A convenient method of drying is to place the coated capsules or tablets on a screen; a screen made up of fine parallel bars with the narrowed edges presented to the capsules is particularly valuable, as it assists in draining off the liquid and gives greater rigidity. The capsules may be agitated while drying but it is preferable that they remain at rest without touching each other. The solvent is allowed to evaporate, and the resin polymerize

5

on the surface giving a resistant coating. With certain resins it is necessary that the capsules be heated to 50° C. for a period of four hours to sufficiently polymerize the material so that it is tack free. Others will polymerize within reasonable time at room temperature. Setting of the silicon containing resin may be expedited by the use of small quantities of a drier such as metallic naphthenates, or others known to the trade. Cobalt naphthenate to the extent of 0.3% by weight of that of the solids in the resin will markedly reduce the drying time of the silicone resins.

Some imperfections will appear in the coating where the capsules contacted each other or where they were supported by the screen during the drying operations, but such imperfections are slight and do not interfere with the salability of the product. It is desirable though, that the number of such contacts be kept at a minimum.

If it is desired to color the capsules, the silicon containing resin coating may be colored with either dyes or pigments. The use of pigments will conceal any imperfections in the capsule itself, and give a remarkably smooth coating. However, by the same token the pigment coating must be perfect to avoid showing defects in such coating. Two or more pigmented coatings may be used to partially allow for contact points being uncoated in each. Recommended practice, however, is to use a comparatively transparent resin coating thus showing any ornamentation in the original capsule and at the same time the contact points will not show except on the most critical inspection.

The silicone resin coating may additionally contain flavors and preservatives. Any of the standard flavors which it is desired to introduce into the capsules to flavor and/or perfume them may be mixed with a compatible solvent, as may the preservatives. Under unusual conditions the gelatin, or contents of a capsule or tablet, may be attacked by various organisms. By the introduction of a preservative such as methyl-p-hydroxy-benzoate or propyl-p-hydroxy-benzoate or other acceptable preservatives, the shelf-life under adverse conditions may be prolonged. The preservative is concentrated in the external surfaces where disintegration might otherwise begin. Flavors and odors such as methyl salicylate or coumarin may be introduced as may any other suitable flavor, the choice is strictly one of aesthetic appeal. By concentrating the flavor on the outside of the capsule a smaller quantity of flavor can be used to give the desired aroma, and the main portion of the medicinal substance will not have such flavor, color, odor or preservative necessarily admixed therewith.

EXAMPLE 1

Hard gelatin capsules

Commercial capsules known as "Vi-Ferrin," a commercial two-piece hard shell capsule containing vitamins, iron, and liver concentrates were dipped into a 3% solids in isopropanol solution of a polymerizing silicone resin, commercially known as Dow-Corning silicone 804. This resin is a comparatively short chain silicone resin containing both phenyl and methyl substituents on the silicon atoms, of comparatively low viscosity and pale colored. The material dries at room temperature to a tack free condition in less than 24 hours, without the addition of additional drier. The capsules were allowed to remain in the solu-

6

tion for approximately 2 to 3 minutes (the time being one of convenience in operation rather than critical), removed, allowed to drain, spread on a wire screen so that the capsules were in the main not in contact with each other, and allowed to air dry at room temperature overnight. As compared with the untreated capsules, the treated capsules were glossier, were tack free, possessed no odor and were tumbled in a half filled commercial container, namely a small glass bottle, for 2 hours without dust, or open capsules appearing. This meant that the capsules could be shipped by commercial carrier without any objectionable dusting or separation with consequent loss of contents deleteriously affecting the salability of the product. The odor free characteristic renders the product more commercially acceptable. The capsules were more resistant to abrasion, and were less sensitive to damage from moist fingers or moisture in the air than untreated capsules.

On utilization tests the capsules swelled in cold water; and when tested in gastric juice disintegrated within 15 minutes. This rate of disintegration is, within limits of experimental error, the same as that for the untreated capsules.

EXAMPLE 2

The same resin as in Example 1, sold as a 60% solution in toluene, was cut to 3% solids with acetone. Hard gelatin capsules, the same as in Example 1, were treated in substantially the same manner in the solution. The resultant product was, within the limits of experimental error, observed to be identical with the products produced in the preceding example. This treatment of these capsules gives the advantages of (1) sealing the sleeve preventing the parting of the capsules; (2) preventing the caking of hygroscopic ingredients; (3) preventing the odor from escaping from the contents; and (4) preventing dusting in the bottle during shipping.

EXAMPLE 3

Tablets

Anti-acid tablets sold commercially as "Aciban," the preparation and properties of which are disclosed in detail in Patent No. 2,362,386, to W. L. Lipschitz, were treated by dipping into a solution of Dow-Corning silicone 804 in a 3% solids in isopropanol for between two and three minutes, removed, drained and allowed to air dry overnight. The tablets were compared with untreated tablets. When placed in a half filled glass bottle and shaken as such tablets are shaken by commercial transit for a period of 10 minutes, the untreated tablets were very dusty and the inside of the bottle covered with a dust film rendering the tablets less commercially acceptable. The treated tablets had a smooth surface without chips before and after tumbling. There was no discernible difference in the appearance of the tablets before and after tumbling and there was no trace of dusting in the bottle.

The preferred method of administration for these tablets is by chewing. On a chewing test there was no discernible difference between the treated and the untreated tablets. The taste of the treated tablets was the same as the taste of the control. The treated tablets disintegrated in cold water within 2 hours, with no effective difference from the rate and properties of disintegration of the untreated tablets used for control.

EXAMPLE 4

An additional sample of the same tablets was treated with a 6% solids solution of the same silicone in acetone under the conditions otherwise the same. After over-night drying the tablets were dust free and exhibited the same properties as exhibited by the tablets in Example 3.

These examples showed the treatment of the tablet to prevent dusting through handling and shipping and to have improved the surface smoothness and appearance of the tablets.

EXAMPLE 5

A sample of the same resin as in Example 1 was prepared as a 3% solids solution by dilution with acetone. Soft gelatin capsules containing a multiple vitamin and mineral preparation including thiamin, vitamin A, vitamin D, niacinamid, calcium phosphate, ferrous sulphate, magnesium sulfate, riboflavin, ascorbic acid and folic acid as powders were prepared. These capsules were allowed to dry until the gelatin films in the capsule had a comparatively low moisture content and then were dipped in the solution of the silicone. The capsules after dipping between 2 and 3 minutes were placed on a screen and allowed to dry for 4 hours at room temperature. The resulting capsules were glossy, tack free with no residual odor from the solvent and the original odor of the thiamin, vitamin A, vitamin D, vitamin E and other contents was confined. The capsules were of pleasing appearance, were water-repellent, and when stored in bottles possessed no appreciable odor.

On utilization test, as compared with the identical capsules which had not been coated, it was found that these capsules swelled when submerged in cold water the same as the uncoated, and disintegrated in gastric juice at 37° C. within 15 minutes, the same as the uncoated capsules. The effect of the coating can be seen by observing the disintegration or the swelling in water. The coated capsules apparently have the coating penetrated in spots which assists in the water penetrating under and flaking off the coating. After once observing the phenomenon it is easy to distinguish their method of disintegration. The time of disintegration is not appreciably altered.

EXAMPLE 6

Capsules prepared as in Example 5 were permitted to air dry overnight at room temperature and were stored for several weeks. Tests and observation of the properties were essentially the same as those in the preceding example.

EXAMPLE 7

Capsules prepared as in Example 5 were air dried at 50° C. for 2 hours. After allowing the capsules to resume room temperature they were tested and found to exhibit the same properties as those obtained in Example 5. After storage for several weeks the capsules exhibited the same properties and when checked for stability of vitamin content it was found that there had been no appreciable change in potency.

EXAMPLE 8

The silicone resin known as Dow-Corning silicone 803 was diluted to a 2% solution in toluene. The dry soft gelatin capsules, as in the preceding example, were dipped therein for 2 to 3 minutes, drained and allowed to air dry for 4

hours. The capsules remained tacky. The capsules were then placed in an oven at 50° C. for 2 hours giving a tack free, glossy film, possessing substantially the same characteristics as the capsules of Example 5. This silicone is a more highly polymerized silicone resin than that used in the preceding examples, and accordingly, it requires more rigorous condition to be cured.

EXAMPLE 9

The silicone sold commercially as General Electric silicone No. 9980, a silicone containing approximately a 50/50 mixture of methyl and phenyl radicals with markedly less than a total of two such radicals per silicon atom, polymerized to a medium viscosity as a 50% solution was diluted to a 4% solution with toluene. Soft gelatin capsules containing a multiple vitamin preparation were dipped therein by a single rapid immersion. The capsules were allowed to drain and were cured at 50° C. for 2 hours. The resultant capsules were tack free, glossy and exhibited the desired characteristics more fully explained in conjunction with Example 5.

EXAMPLE 10

Soft gelatin capsules were exposed to the vapor of a mixture of methyl silicon chloride consisting mainly of methyl silicon trichloride and dimethyl silicon dichloride, as disclosed in the patent to Patnode, No. 2,306,222. The treated capsules were exposed to the fumes of concentrated ammonia to insure complete replacement of all chlorine and neutralization of the acid produced. The capsules as thus treated had a protective coating which was water repellent and tack free. The capsules disintegrated readily in water or in gastric juice. However, the soft gelatin capsules were not as glossy as those coated with a solution as described in Examples 5 to 9.

EXAMPLE 11

A silicone resin may be prepared in accordance with the general instructions of Patent No. 2,258,222 to Rochow, except using a ratio of methyl plus phenyl to silicon of the order of 1.2 to 1, the mixture subjected to the Grignard reaction, hydrolyzed and partially polymerized by boiling in toluene until a satisfactory viscosity is obtained, of about 1 poise at 25° C. (c. g. s.). Such a solution when cooled, diluted to a 4% solids in acetone solution, and cobalt naphthenate, to the proportion of .3% based on the solids in the solution, added gives a resultant solution to be used for the coating of soft gelatin capsules containing a hygroscopic liver preparation. Capsules dipped in such a solution for approximately 3 minutes (longer time may be used but is not necessary) were placed on screens and allowed to dry. The capsules were heated to 50° C. for 6 hours, and found to possess a tack free, glossy finish which protected the contents from moisture and prevented the escape of odor. When testing for therapeutic efficiency there was no discernible distinction between these so treated tablets and the untreated tablets.

EXAMPLE 12

The solution such as that of Example 11 was used for treating "Aciban" tablets for a period of 30 seconds. The tablets were removed, allowed to drain and cured at the temperature of 55° C. for 4 hours. The resulting tablets had a hard, dust free finish which stood up under shipping and other conditions. When testing for thera-

peutic efficiency there was no discernible distinction between these treated tablets and the untreated tablets.

EXAMPLE 13

Hard gelatin capsules containing a multiple vitamin preparation including riboflavin, thiamin, vitamin A, vitamin D, ascorbic acid, niacinamid, and pyridoxine, as a powder, were dipped for 10 minutes in a solution prepared in accordance with Example 11. The capsules were removed, allowed to drain, cured at 50° C. for 3 hours. As so treated the capsules possess a hard, tack free, glossy finish. The capsules do not dust nor come apart and possess an unimpaired therapeutic efficiency.

EXAMPLE 14

Soft gelatin capsules containing a therapeutic dose of vitamins, including riboflavin, thiamin, vitamin A, vitamin D, niacinamid, calcium phosphate, ferrous sulphate, magnesium sulfate and folic acid, such as sold commercially under the trade-name of "Perfolin," were dipped in a solution containing 3.2% of silicone solids in isopropanol, having added thereto additionally 0.2% methyl salicylate, 0.02% coumarin and 0.08% each of methyl-p-hydroxy-benzoate and propyl-p-hydroxy benzoate. After dipping the capsules therein, they were placed on a wire screen, shaken to remove the excess fluid and allowed to dry at room temperature for 24 hours. The capsules were found to have a glossier finish, were tack free, had a pleasant smell, all unpleasant odors being masked, and were found to swell in cold water and disintegrate in gastric juice at 37° C. in 15 minutes. It was found that the thus coated capsules in use disintegrated in the same time as the uncoated capsules within limits of experimental observation.

Because of the swelling of the capsules and the method of the disintegration it is not readily possible to determine the exact point at which a capsule can be said to have disintegrated, but if the same standards are taken for the coated and the uncoated capsules there will be found to be no appreciable difference in their disintegration time.

From the commercial standpoint, isopropanol appears to be a solvent of choice. Acetone may cause an explosion hazard, methanol is toxic and must be thoroughly removed, ethanol is unduly expensive because of peculiar tax difficulties within the United States, and the higher alcohols are of course, more difficult to remove by evaporation, and some of them have unpleasant effects if small quantities are ingested.

Other silicone resin solutions can be used as well as other concentrations. If more dilute concentrations are used more than one dipping may be required. If more concentrated solu-

tions are used an unduly large proportion of the expensive silicone resin may be used and it is possible by repeated dipping or by the use of a viscous concentrated solution to obtain such a hard coating that the capsules do not readily dissolve. Within these generalized limitations any of the silicone resins, which cure under conditions which do not deleteriously affect the contents, will be found to possess the above mentioned desired properties.

These silicon containing resins appear to have the unique quality of preventing the escape of odor and protect the capsule contents from the effects of moisture without preventing water or an aqueous solution in the liquid phase from penetrating the coating to release the contents for a beneficial therapeutic effect.

Having thus described certain embodiments of our invention, we claim:

1. As a new article of manufacture a medicament surrounded by a moisture and odor resistant layer of a silicone resin which is tack free and which upon ingestion permits ready disintegration and assimilation of such article.
2. A hard gelatin capsule possessing a coating consisting of an organo silicone resin whereby the capsule is rendered moisture repellent and odor free.
3. A tablet possessing a coating consisting of an organo silicone resin whereby the tablet is rendered moisture repellent and odor free.
4. A soft gelatin capsule possessing a coating consisting of an organo silicone resin whereby the capsule is rendered moisture repellent and odor free.

ERNEST C. YEN.
FRANK E. STIRN.

REFERENCES CITED

- The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
2,205,111	Volwiler	June 18, 1940
2,306,222	Patnode	Dec. 22, 1942
2,329,632	Marsden	Sept. 14, 1943
2,371,050	Hyde	Nov. 6, 1945
2,386,259	Norton	Oct. 9, 1945
2,386,466	Hyde	Oct. 9, 1945
2,389,477	Wright	Nov. 20, 1945
2,394,642	Strain	Feb. 12, 1946
2,395,550	Iler	Feb. 26, 1946
2,408,822	Tanis	Oct. 8, 1946
2,410,417	Andersen	Nov. 5, 1946
2,424,853	Safford	July 29, 1947
2,470,772	Haas	May 24, 1949

OTHER REFERENCES

- Paint Manufacture, July 1947, page 248.